acids 246 to 491; the VP1 protein of HAV corresponding to amino acids 492 to 791; the P2A protein of HAV corresponding to amino acids 792 to 980; the P2B protein of HAV corresponding to amino acids 981 to 1087; the P2C protein of HAV corresponding to amino acids 1088 to 1422; the P3A protein of HAV corresponding to amino acids 1423 to 1496; the P3B protein of HAV corresponding to amino acids 1497 to 1519; the P3C protein of HAV corresponding to amino acids 1520 to 1738, wherein the antigenically reactive peptide binds to an antibody specifically antigenically reactive with a peptide selected from the group consisting of SEQ ID NOS: 11-72 and conservative variations thereof.

71. (Amended) The antigenically reactive peptide of claim 70, wherein the antigenically reactive peptide binds to an antibody specifically antigenically reactive with a peptide selected from the group consisting of SEQ ID NOS: 11-72 and conservative variations thereof.

72. (Amended) The antigenically reactive peptide of Claim 70 wherein the antigenically reactive peptide has an amino acid sequence selected from the group consisting of SEQ ID NOS: 11-72 and conservative variations thereof.

REMARKS

Claims 70-72 are pending in this application after the withdrawal of claims 1, 69 and 74-76, due to the Applicants' election of Group II, and the Examiner's withdrawal of claim 73 as being directed to a nonelected species. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with

markings to show changes made." No new matter is believed added. Support for these amendments can be found throughout the specification, as set forth below. In light of the following remarks, Applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

Applicants submit herewith a copy of an executed Declaration acknowledging the filing of and claiming priority to Provisional Application No. 60/015,644. Submission of this document along with the above-indicated Amendment to the specification to reference both the Provisional Application No. 60/015,644 and international application PCT/US97/06891 is believed to place the current application in compliance with conditions for receiving the benefit of the filing date of the Provisional Application under 35 U.S.C. § 119(e).

I. Rejection under 35 U.S.C. § 112, second paragraph

Claims 70-72 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly not particularly pointing out and distinctly claiming the subject matter which the Applicants regard as their invention. Specifically, the Office Action states that recitation of an "HAV" peptide is improper and suggests that the unabbreviated name be written-out in the claim. The Office Action states that recitation of an amino acid sequence which is "substantially similar," and "similar" are relative terms that are not defined in the claim, that the specification does not provide a standard for ascertaining the requisite degree of similarity and that one of ordinary skill in the art would not be apprised of the scope of the invention. The Office Action alleges that use of the term "portion" renders the claim indefinite as the metes and

bounds of portion are not taught in the disclosure. Furthermore, the Office Action alleges that it is unclear whether the portion claimed is a portion of the HAV polyprotein corresponding to the P2A protein or a portion of the P2A protein. The Office Action states that the term about, when referring to the HAV protein as corresponding to AA "792 to about 980," renders the claim indefinite because the upper limit of the AA range cannot be ascertained. Furthermore, the claim recites "conservative variations thereof." The Office Action asserts that the phrase "conservative variations thereof" is not defined in the disclosure. Finally, the Office Action indicates that it is unclear to what sequence "amino acids 792 to about 980" is referring in the absence of either a SEQ ID NO: or a sequence name which is supported by a specifically recited sequence in the specification.

Applicants submit that claims 70-72, particularly as amended, are not indefinite and do particularly point out and distinctly claim the subject matter of the invention. Specifically, claim 70 has been amended so as to recite "hepatitis A virus (HAV)" as was suggested by the Examiner. In regard to the Office Action's objection to the use of "substantially similar to a portion" for allegedly rendering the claim indefinite, Applicants first refer the Examiner's attention to page 4, line 42 - page 5, line 26 of the specification wherein an HAV peptide comprising "...an amino acid sequence which is substantially similar to a portion of the P2A portion of HAV..." is described as being capable of "...bind(ing) to an antibody specifically immunoreactive with a peptide selected from..." a defined group of peptides. The defined group of peptides from which the peptide which is specifically immunoreactive with an antibody in this case consists of SEQ ID NOS:11-72 and conservative variations thereof. Applicants submit that this passage of the specification as filed adequately defines

the term "substantially similar" and that use of the term does not render the claim indefinite as the criteria for what is a "substantially similar" sequence is clearly set forth in the specification. Specifically, Applicants submit that a substantially similar sequence is one which, when present, binds to an antibody specifically immunoreactive with a peptide selected from the group of peptides provided in the specification, namely, SEQ ID NOS:11-72 and conservative variations thereof. In like fashion, amended claims 70-72 reciting "antigenically reactive," rather than "immunoreactive" ...peptides clearly preserve the established meaning of the term "substantially similar" and yet further clarifies the properties of the peptides and the relationship between the peptide of claim 70, the recited antibody and the peptide selected from the group consisting of SEQ ID NOS:11-72. Applicants request removal of this objection.

In regard to the Office Action's assertion that the term "portion" renders claim 70 indefinite for failing to teach "the metes and bounds of such a portion," Applicant submits that the claim as written is definite. Specifically, the claim recites an "...immunogenic peptide comprising an amino acid sequence... ...similar to a portion of an HAV protein selected from the group consisting of... ...the P2A protein..." In other words, it states that the sequence comprised in the peptide is similar to a portion of a protein selected from a group of HAV proteins. This indicates clearly that the amino acid sequence is similar to a portion of whatever protein is selected, not that the portion selected consists of the entire selected protein. Similarly, the corresponding description in the specification at page 4, line 43, states that the amino acid sequence "...is substantially similar to a portion of the P2A protein of HAV..." Furthermore, Applicants submit that this claim drawn to "...a portion of the P2A protein...," as it is

described in the Office Action, does not render the claim indefinite as anyone of skill in the art is reasonably apprised of the invention. Specifically, Applicants submit that as a portion of an item indicates any fraction up to, and including, the complete item, it would be clear to anyone of skill in the art that a portion of the P2A protein means a fraction or fragment of the P2A protein. Thus it is clear to the skilled person what this term means as used in its context. Further, Applicants submit that a specific recitation of each and every sequence of this aspect of the invention is unnecessary to comply with the requirements of 35 U.S.C. § 112. Applicants request removal of this objection.

In regard to the Office Action's assertion that use of the term "about," when referring to HAV proteins' sequences, renders claim 70 indefinite because the upper limit of the amino acid range cannot be ascertained, Applicants submit that the claim is not rendered indefinite by this usage of the term "about" because it is to the specified proteins, e.g., P2A, and not to the sequence numbering, e.g., amino acid residues 792 to about 980, to which the claim refers when defining the peptides of the invention. Thus, while the use of the term "about" refers to an approximate location in the polypeptide which corresponds to the HAV proteins from which the peptides of the invention are derived, the proteins themselves are specifically identified by name. As such is the case, Applicants submit that even without a recitation of the specific amino acid residues in the claim, the recitation of the different proteins provide adequate, indeed identical, description. However, for the sake of greater clarity, Applicants have amended the claims by deleting "about" to comply with the Examiner's comments. Applicants request removal of this objection.

In regard to the Office Actions' assertion that the term "conservative variations thereof" is not defined in the disclosure, the term "conservatively modified variations" (page 13, lines 14-19) is used in the specification to describe nucleic acids which encode amino acid sequences with low levels of changes in the encoded amino acid sequence. Furthermore, the application includes "conservative substitution tables" which provide examples of conservative substitutions (page 13, lines 19-28). Together with the knowledge in the art, these teachings in the specification render the intended meaning of conservative variations of amino acid sequence definite to those of skill in the art. Thus, the term "conservative variations," when used in context of encoded amino acid sequence, clearly conveys to those of skill in the art that the amino acid sequences were those encoded by, or which could be encoded by, "conservatively modified variations" of nucleic acid sequences as defined in the specification. Applicants request removal of this objection.

In regard to the numbering system of the recited sequences of polypeptides, Applicants refer the Examiner to the well-established nomenclature for the HAV polyprotein, and proteins formed from the polyprotein, wherein the numerical residue identifiers for the polyprotein are retained for the processed proteins. Further, for each of the proteins recited in the specification, the bounds of each protein in terms of the amino acid sequence numbers are listed. Most notably, the bounds of each are listed in the titles of Tables 2-11 corresponding to the HAV proteins, e.g., see Table 5 (page 52), wherein the title recites *inter alia* "...the P2A protein (792-980 aa)..." Further, as the claims recite proteins known to be derived from the HAV polyprotein, Applicants submit that the use of polyprotein numbering scheme

to define the antigenically reactive proteins would be clear to the skilled person in the art. Applicants request removal of this objection.

II. Rejection under 35 U.S.C. § 103

Claims 70-72 are rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Chiron Corporation (EPA 0 199 480). Specifically, the Office Action construes the present invention to be an "isolated immunogenic peptide comprising an amino acid sequence corresponding to AA 792-980 of the polyprotein of HAV (the P2A protein) which binds to an antibody that is specifically immunoreactive with a peptide selected from the group consisting of SEQ ID NO:11- SEQ ID NO:72." The Office Action asserts that the invention is unpatentable over Chiron because Chiron teaches the entire genome of the HAV and teaches epitopes which are immunogenic. Specifically, Chiron teaches the predicted P2A protein as roughly corresponding to AA 837-980 of the polyprotein and teaches a preferred immunogenic peptide as derived from AA 792-848. From this, the Office Action alleges that one of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have made the presently claimed invention.

Applicants note that while Chiron discloses the entire genome of HCV and recites a preferred immunogenic peptide as derived from AA 792-848, Chiron does not and could not provide any immunogenic peptide derived from AA 792-848. Chiron neither made nor tested any peptide corresponding to AA 792-848 in conjunction with the cited application. In fact, at the time the present invention was made, it was well-established that the nonstructural proteins of HAV, including the P2A

protein, were not immunogenic (Khudyakov et al., *Virology* 260: 260-272 (1999) and references cited therein, Attached as Exhibits A-D). In light of these observations, one of ordinary skill in the art at the time the invention was made would not have even expected to have been able to produce the invention disclosed in Chiron. Thus, given the teaching of Khudyakov et al., Chiron does not provide even the minimal requirements of a *prima facie* case of obviousness, namely, it does not provide a reasonable expectation of success. Furthermore, the claims, as amended to recite antigenically reactive peptides, are further distinguished from the teachings of Chiron as Chiron teaches immunogenic peptides. Support for the amendment of the claims to recite antigenically reactive peptides can be found throughout the application, but most notably in the Examples (pages 40-56) wherein the specific sequences are examined in assays to determine antigenic reactivity and the results of those assays are described. Applicants request removal of this rejection.

Applicants have also amended claim 70 to correct an error of a clerical nature. As filed, the claim recited incorrectly the corresponding amino acids for the P3B protein. Support for the amendment of claim 70 to recite "...the P3B protein of HAV corresponding to amino acids 1497 to about 1519;..." can be found in the title for Table 9 (page 54). Applicants respectfully request entry of this amendment.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No additional fees are believed to be warranted; however, the Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 14-062.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — Date: 8-15-01

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

70. (Amended) An isolated, [immunogenic HAV] antigenically reactive hepatitis A virus (HAV) peptide, [said immunogenic] antigenically reactive peptide comprising an amino acid sequence which is substantially similar to a portion of an HAV protein selected from the group consisting of the VP3 protein of HAV corresponding to amino acids 246 to [about] 491; the VP1 protein of HAV corresponding to amino acids 492 to [about] 791; the P2A protein of HAV corresponding to amino acids 792 to [about] 980; the P2B protein of HAV corresponding to amino acids 981 to [about] 1087; the P2C protein of HAV corresponding to amino acids 1088 to [about] 1422; the P3A protein of HAV corresponding to amino acids 1423 to [about] 1496; the P3B protein of HAV corresponding to amino acids [1423] 1497 to [about 1496] 1519; the P3C protein of HAV corresponding to amino acids 1520 to [about] 1738, wherein the [immunogenic] antigenically reactive peptide binds to an antibody specifically [immunoreactive] antigenically reactive with a peptide selected from the group consisting of SEQ ID NOS: 11-72 and conservative variations thereof.

71. (Amended) The [immunogenic] antigenically reactive peptide of claim 70, wherein [said immunogenic] the antigenically reactive peptide binds to an antibody specifically [immunoreactive] antigenically reactive with a peptide selected from the group consisting of SEQ ID NOS: 11-72 and conservative variations thereof.

72. (Amended) The [immunogenic] antigenically reactive peptide of Claim 70 wherein the [immunogenic] antigenically reactive peptide has an amino acid sequence selected from the group consisting of SEQ ID NOS: 11-72 and conservative variations thereof.